

## **REMARKS**

### **I. Background**

The present amendment and remarks are in response to the Office Action mailed September 20, 2007. Claims 13-32 were pending in the application at the time of the Office Action. Applicant has amended claims 13 and 17-19, 24, and 31-32. Applicant has cancelled claims 27-28. New claims 33 and 34 have been added. As such, claims 13-26 and 29-34 are currently pending for consideration on the merits.

Reconsideration of the claims is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited reference and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, Applicant requests that the Examiner carefully review any reference discussed below to ensure that Applicant's understanding and discussion of the references, if any, is consistent with the Examiner's understanding.

### **II. Proposed Claim Amendments**

The amendments and new claims are fully supported by the specification and claims as originally filed. More particularly, the amendment to claim 13 is supported by at least paragraphs [0044-0051]<sup>1</sup>, and the amendments to claims 24, 31, and 32 are supported by the Examples that were performed on human urothelium. New claims 33 and 34 are fully supported by paragraph [0051]. Thus, Applicant respectfully submits that the amendments to the claims do not introduce new matter and entry thereof is respectfully requested.

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<sup>1</sup> (PG-Pub 2005/0233445).

### **III. Rejection on the Merits**

#### **A. 35 USC § 112 First Paragraph**

The Office Action rejects claims 27-28 under 35 USC § 112, first paragraph, failing to comply with the written description requirement. Applicant has cancelled claims 27-28 rendering the rejection moot.

#### **B. 35 USC § 112 First Paragraph**

The Office Action rejects claims 24-32 under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Office Action recites MPEP § 2172.01. After a review of MPEP § 2172.01, Applicant respectfully asserts the rejection is improper because cited section in the MPEP recites, “a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 USC § 112, for failure to point out and distinctly claim the invention. See *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976). Applicant respectfully asserts that the claims sufficiently interrelate the essential elements of the invention being claimed. Additionally, Applicant respectfully requests identification of the allegedly omitted essential element. Moreover, Applicant specifically indicated that claims 24-32 are fully supported by the specification at paragraphs [0036-0052]<sup>2</sup> in the previous Office Action.

Applicant respectfully asserts that the claimed method is substantially and patentably distinct from *Zhang et al* (In vitro Cell. Dev. Biol.-Animal 2001) and/or the Southgate reference. As such, these references cannot be construed in a manner so show the presently claimed invention is missing an essential method step or component.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection under 35 USC § 112, second paragraph.

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<sup>2</sup> (PG-Pub 2005/0233445)

**C. 35 USC § 102**

The Office Action rejects claims 13, 15, 17-19, and 21-32 under 35 USC § 102(b) as being anticipated by the article by *Zhang et al* (In vitro Cell. Dev. Biol.-Animal 2001). Applicant respectfully traverses the rejection because the Office Action has not established that *Zhang* teaches each and every claim element in the presently pending claims.

In accordance with Applicant's understanding, *Zhang* discloses the cultivation of rat urothelial cells (RUC) in a range of growth media, including a conditioned medium "KSFM-CM". Also, *Zhang* teaches that cells could be maintained in such medium for up to 18 passages (see Abstract, and also paragraph 2 of the Introduction). However, the primary culture of the RUC is in the serum-free medium "KSFM" (see paragraph 2 of the introduction, and the section entitled "Primary Culture of RUC" on page 425). The primary culture is then taught to be propagated in a mixture of conditioned medium (CM) derived from Swiss 3T3 cell culture supernatant and KSFM (CM-KSFM). and maintained for 18 passages. As such, *Zhang* reports "urothelial stratification" when these cells are then grown on the "KSFM-CM" medium. However, KSFM-CM is not considered a serum-containing medium because of at least the following: the CM is prepared by incubating Swiss 3T3 cells in DMEM for 24 hours, and nothing in *Zhang* indicates the DMEM is supplemented with serum during this process (see page 422, first column, second paragraph); the CM is not prepared with serum; or even if CM was prepared with DMEM and serum, which it wasn't, the Swiss 3T3 cells necessarily utilize the components of the serum thereby changing the chemical and substance composition of the cell supernatant such that the CM does not include "whole serum." Additionally, in the studies shown in Table 2, the CM was described as being "enriched with 10% FBS" (see page 427, first paragraph and was an unsuitable media) indicating that CM does not include serum. The CM enriched with 10% FBS was shown to be unsatisfactory. Thus, *Zhang* does not teach or disclosure that the cells were "passaged through a nutrient medium containing serum" before being redispersed and going on in another "nutrient medium containing serum" in order to form stratified, terminally-differentiated urothelium as recited in claims 13 and 24.

While *Zhang* reports the apparent formation of "stratified" and "differentiated" multilayer structures from the RUC (see e.g. abstract), no objective evidence of differentiation is presented in the paper. The only marker used is the detection of cytokeratin 17, which is not a urothelial

differentiation marker. For example, Figure 7a of the *Zhang* shows that C17 is expressed through all layers of control rat urothelium *in situ*. On reason why the authors might have produced what appears to be stratified cells is that there could have been a spontaneous transformation of the cells leading to immortalization. This is a known feature of rodent epithelial cells, and the cells produced are no longer normal. The long period for which the authors were able to maintain the cultures (18 passages) is strongly indicative of such a spontaneous transformation. The number of passages obtained with the CM supplemented medium is additional evidence that CM does not include serum. In fact, *Zhang* teaches that when RUC cells were placed into standard medium containing serum, the cells showed low plating efficiency, poor growth characteristics, a limited potential for cell division, and failed to differentiate *in vitro* (see page 427, last paragraph through 428 first paragraph). This teaches away from the presently claimed invention.

Accordingly, Applicant respectfully asserts that *Zhang* does not teach each and every element of the presently claimed invention recited in claims 13 and 24. More particularly, *Zhang* is completely devoid of teaching or suggesting a “method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium,” as recited in claim 13. *Zhang* is also completely devoid of teaching or suggesting dispersing urothelial cells of the primary culture into a first differentiation cell culture medium that includes whole serum; culturing the urothelial cells in the first differentiation culture medium to form a secondary cell culture having aggregated urothelial cells; dispersing and disaggregating the aggregated urothelial cells into a second differentiation cell culture medium that includes whole serum; and culturing the urothelial cells in the third culture medium so as to form stratified, terminally-differentiated mammalian urothelium,” as recited in claim 24. In part, this is because *Zhang* is completely devoid of any teaching that urothelium cells can be passaged through a first media containing serum before being redispersed and being cultured into a second media containing serum in order to form stratified, terminally-differentiated urothelium. Thus, *Zhang* does not teach each and every element of the presently claimed invention recited in claims 13 and 24.

Since *Zhang* does not teach each and every claim element, *Zhang* does not anticipate the

presently claimed invention recited in claims 13 and 24. Since claims 13, 15, 17-19, 21-26, and 29-32 depend from claims 13 or 24, such claims include the same claim elements and are allowable for at least the same reasons that claims 13 and 24 are allowable. Thus, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e) with respect to *Zhang*.

The Office Action rejects claims 13, 15, and 23 under 35 USC § 102(b) as being anticipated by the article by *Liebert et al.* (Differentiation 1997). Applicant respectfully traverses the rejection because the Office Action has not established that *Liebert* teaches each and every claim element in the presently pending claims.

In accordance with applicant's understanding, *Liebert* teaches that urothelial cells can be cultured in low-calcium, serum-free media to propagate urothelial cells, and the cells can then be induced to differentiate by replacing the media with KSM or MEM containing serum (see page 178 first paragraph; Methods section first paragraph). However, the method does not teach that the cells isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum. In fact, nothing the *Liebert* teaches or suggests that you can disperse urothelial cells into any medium containing serum in order to produce stratified, differentiated urothelium, and thereby does not teach that urothelial cells being cultured in media containing serum can be redispersed into a second medium containing serum. Further, *Liebert* does not teach that such processing can form stratified, terminally-differentiated urothelium. As discussed in the present application at paragraphs [0017-0018], the method disclosed in *Liebert* does not result in the high transepithelial resistance that is characteristic of stratified, terminally-differentiated urothelium.

Accordingly, Applicant respectfully asserts that *Liebert* does not teach each and every element of the presently claimed invention recited in claim 13. More particularly, *Liebert* is completely devoid of teaching or suggesting a "method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium," as recited in claim 13. In part, this is because *Liebert* is completely devoid of any teaching that urothelium cells can be passaged through a first media containing serum before being redispersed and being cultured into a second media containing serum in order to form stratified, terminally-differentiated

urothelium. Thus, *Liebert* does not teach each and every element of the presently claimed invention recited in claim 13.

Since *Liebert* does not teach each and every claim element, *Liebert* does not anticipate the presently claimed invention recited in claim 13. Since claims 15 and 23 depend from claim 13, such claims include the same claim elements and are allowable for at least the same reasons that claim 13 is allowable. Thus, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e) with respect to *Liebert*.

The Office Action rejects claims 13-15, 17, 18, and 23 under 35 USC § 102(b) as being anticipated by the article by *Scriven et al.* (The Journal of Urology 1997). Applicant respectfully traverses the rejection because the Office Action has not established that *Scriven* teaches each and every claim element in the presently pending claims.

In accordance with Applicant's understanding, *Scriven* discloses that urothelial cells can be obtained from tissue by being detached from the stroma, disaggregated in collagenase, and seeded into a serum-free medium (see page 1148 first paragraph). The urothelial cells in the serum-free media can then be resuspended in medium and replated into Primaria flasks or used in tissue reconstitution experiments. At no time does *Scriven* teach or suggest that the medium can include serum when used with only urothelial cells. The urothelium cells maintained in the serum-free media are described to be used by being seeded onto a de-epithelialized basement membrane. Also, *Scriven* teaches that tissue pieces of 0.5 to 1 cm<sup>2</sup> can be grown in serum-containing medium with the urothelial side up. However, *Scriven* does not teach or suggest the growth of urothelial cells in a serum-containing medium, and then redispersal into another serum-containing medium. While *Scriven* does disclose the use of serum-containing medium, this medium is used for the urothelial organ culture that is subsequently de-epithelialized to provide stroma on which to culture urothelial cells (see page 1148, section entitled "Organ Culture"). The urothelial cells themselves are grown on keratinocyte serum-free medium (see page 1148, section entitled "Tissue Collection and Processing").

Applicant respectfully asserts that *Scriven* does not teach each and every element of the presently claimed invention recited in claim 13. More particularly, *Scriven* is completely devoid of teaching a "method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a

first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium,” as recited in claim 13. In part, this is because once the urothelium cells of *Scriven* are cultured in a media containing serum, such cells are not dispersed into a second media containing serum. Thus, *Scriven* does not teach each and every element of the presently claimed invention recited in claim 13.

Since *Scriven* does not teach each and every claim element, *Scriven* does not anticipate the presently claimed invention recited in claim 13. Since claims 14-15, 17, 18, and 23 depend from claim 13, such claims include the same claim elements and are allowable for at least the same reasons that claim 13 is allowable. Thus, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e) with respect to *Scriven*.

#### **D. 35 USC § 103**

The Office Action rejects claim 16 under 35 USC § 103(a) as being obvious over the articles by *Zhang*, *Liebert*, or *Scriven* in view of *Seiji* *et al.* (U.S. Patent No. 4,654,304). Applicant respectfully asserts that the Office Action has not established a *prima facie* case of obviousness because the proposed combination of references (e.g., *Zhang*, *Liebert*, or *Scriven* in combination with *Seiji*) does not teach or suggest each and every element of the presently claimed invention.

In accordance with Applicant’s understanding, *Seiji* only teaches or suggests cell culture compositions that promote cell growth, but not cell differentiation. In fact, *Seiji* does not teach a cell culture media that promotes cell differentiation. Cell growth is an entirely different process from cell differentiation. Thus, *Seiji* does not teach the use of adult bovine serum for cell differentiation, and a skilled artisan would not consult *Seiji* in preparing a cell culture media that promotes cell differentiation.

The foregoing discussions of *Zhang*, *Liebert*, and/or *Scriven* are applicable to this rejection, and are hereby incorporated into this remark by specific reference. Applicant respectfully asserts that *Seiji* does not cure the deficiencies of *Zhang*, *Liebert*, and/or *Scriven*, which were discussed above. That is, *Seiji* does not teach the claim limitations of claim 13. Applicant asserts that the combination of *Zhang*, *Liebert*, or *Scriven* with *Seiji* does not teach or suggest a “method of production of stratified, terminally-differentiated mammalian urothelium

in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium,” as recited in claim 13. Thus, the combination of *Zhang*, *Liebert*, or *Scriven* with *Seijiro* does not teach or suggest each and every claim element of the claim 13.

Since the combination of references (e.g., *Zhang*, *Liebert*, or *Scriven* in combination with *Seijiro*) does not teach or suggest each and every element of the presently claimed invention, a *prima facie* case of obviousness has not been established with respect to claim 13. Since claim 16 depends from claim 13, claim 16 includes the same claim elements and is allowable for at least the same reasons claim 13 is allowable. Thus, Applicant respectfully requests withdrawal of the rejection of claim 16 under 35 U.S.C. § 103(a).

The Office Action rejects claim 20 under 35 USC § 103(a) as being obvious over *Zhang* in view of *Judd et al.* (U.S. Patent No. 6,692,961). Applicant respectfully asserts that the Office Action has not established a *prima facie* case of obviousness because the proposed combination of *Zhang* and *Judd* does not teach or suggest each and every element of the presently claimed invention.

In accordance with Applicant’s understanding, *Judd* teaches the development of defined growth media (i.e. not containing serum) for the propagation of epithelial cells, but does not teach the defined media can be used for cell differentiation. As stated above, cell growth is an entirely different process from cell differentiation, and cell differentiation has different media requirements. Thus, *Judd* does not teach the use of a defined medium for cell differentiation, and a skilled artisan would not consult *Judd* in preparing a cell culture media that promotes cell differentiation.

The foregoing discussion of *Zhang* is applicable to this rejection, and is hereby incorporated into this remark by specific reference. Applicant respectfully asserts that *Judd* does not cure the deficiencies of *Zhang*. That is, *Judd* does not teach the claim limitations of claim 13, and the combination of *Zhang* and *Judd* is completely devoid of teaching or suggesting a “method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum



to form said urothelium,” as recited in claim 13. Thus, the combination of *Zhang* and *Judd* does not teach or suggest each and every element of the presently claimed invention as recited in claim 13.

Since the combination of *Zhang* and *Judd* does not teach or suggest each and every element of the presently claimed invention, a *prima facie* case of obviousness has not been established with regard to claim 13. Since claim 20 depends from claim 13, claim 20 includes the same claim elements and is allowable for at least the same reasons claim 13 is allowable. Thus, Applicant respectfully requests withdrawal of the rejection of claim 20 under 35 U.S.C. § 103(a).

The Office Action rejects claims 20 and 22 under 35 USC § 103(a) as being obvious over *Liebert* in view of *Judd*. Applicant respectfully asserts that the Office Action has not established a *prima facie* case of obviousness because the proposed combination of *Liebert* and *Judd* does not teach or suggest each and every element of the presently claimed invention.

The foregoing discussions of *Liebert* and *Judd* are applicable to this rejection, and are hereby incorporated into this remark by specific reference. Applicant respectfully asserts that *Judd* does not cure the deficiencies of *Liebert*. That is, *Judd* does not teach the claim limitations of claim 13, and the combination of *Liebert* and *Judd* is completely devoid of teaching or suggesting a “method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium,” as recited in claim 13. Thus, the combination of *Liebert* and *Judd* does not teach or suggest each and every element of the presently claimed invention as recited in claim 13.

Since the combination of *Liebert* and *Judd* does not teach or suggest each and every element of the presently claimed invention, a *prima facie* case of obviousness has not been established with regard to claim 13. Since claims 20 and 22 depend from claim 13, claims 20 and 22 each include the same claim elements and is allowable for the same reasons claim 13 is allowable. Thus, Applicant respectfully requests withdrawal of the rejection of claims 20 and 22 under 35 U.S.C. § 103(a).

The Office Action rejects claims 13-15 and 17-32 under 35 USC § 103(a) as being obvious over the *Cross et al.* (Biochemical Society Transactions 2001) in view of *Zhang*. Applicant respectfully asserts that the Office Action has not established a *prima facie* case of obviousness because the proposed combination of references (e.g., *Cross* in view of *Zhang*) does not teach or suggest each and every element of the presently claimed invention.

In accordance with Applicant's understanding, *Cross* studied the barrier properties of human urothelium where normal human urothelial cell cultures were established and propagated in serum-free media. *Cross* teaches that serum was then introduced into the culture and resulted in stratification. However, nothing in *Cross* teaches that urothelium cells grown in a serum-containing media are redispersed into another serum-containing media.

The foregoing discussion of *Zhang* is applicable to this rejection, and is hereby incorporated into this remark by specific reference. Applicant respectfully asserts that *Cross* does not cure the deficiencies of *Zhang*, which were discussed above. That is, *Cross* does not teach the claim limitations of claim 13. Applicant asserts that the combination of *Zhang* and *Cross* does not teach or suggest a "method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form said urothelium," as recited in claim 13. The combination of *Zhang* and *Cross* is also completely devoid of teaching or suggesting "dispersing urothelial cells of the primary culture into a first differentiation cell culture medium that includes whole serum; culturing the urothelial cells in the first differentiation culture medium to form a secondary cell culture having aggregated urothelial cells; dispersing and disaggregating the aggregated urothelial cells into a second differentiation cell culture medium that includes whole serum; and culturing the urothelial cells in the third culture medium so as to form stratified, terminally-differentiated mammalian urothelium," as recited in claim 24. Thus, the combination of *Zhang* and *Cross* does not teach or suggest each and every claim element of the claims 13 and 24.

Since the combination of *Zhang* and *Cross* does not teach or suggest each and every element of the presently claimed invention, a *prima facie* case of obviousness has not been established with respect to claim 13. Since claims 13-15, 17- 23, 25-27, and 29-32 depends from

claims 13 or 24, and thereby include the same claim elements and are allowable for at least the same reasons claims 13 and 24 are allowable. Thus, Applicant respectfully requests withdrawal of the rejection of claim 13-15, 17-26, and 29-32 under 35 U.S.C. § 103(a).

#### **IV. References Teach Away From Claims**

Applicant respectfully asserts that the art of record recited in the rejections discussed above teach away from the presently claimed invention. In part, this is because the presently claimed invention recites that cells grown in a serum-containing media are redispersed into another serum-containing medium. However, none of the art of record teaches such redispersion from a serum-containing medium into another serum-containing medium. After a reading of the art of record, the skilled artisan would not be motivated to redisperse cells from a serum-containing medium into another serum-containing medium because redispersion of cells constitutes an action that is apparently diametrically opposed to achieving the desired result of an organized, stratified, terminally-differentiated urothelium. Accordingly, the skilled artisan would seek to maintain any structure from the first culture stage, rather than disrupting it by redispersion, and would have no motivation to overturn this technical prejudice.

#### **V. New Claims**

Applicant respectfully asserts that new claims 33-34 are allowable for at least the same reasons claims 13 and 24 are allowable. None of the references recited in the rejections to the claims teaches or suggests the inventions recited in claims 33-34. Thus, Applicant submits that new claims 24-32 are allowable over the references recited in the rejections discussed herein.

### **CONCLUSION**

In view of the foregoing, Applicant respectfully submits that the other rejections to the claims are now moot and do not, therefore, need to be addressed individually at this time. It will be appreciated, however, that this should not be construed as Applicant acquiescing to any of the purported teachings or assertions made regarding the cited art or the pending application, including any Official Notice. Instead, Applicant reserves the right to challenge any of the

purported teachings or assertions made in any action at any appropriate time in the future, should the need arise. Furthermore, to the extent that the Examiner has relied on any Official Notice, explicitly or implicitly, Applicant specifically requests that the Examiner provide references supporting the teachings officially noticed, as well as the required motivation or suggestion to combine the relied upon Notice with the other art of record.

Applicant believes claims 13-26 and 29-34 are in allowable form as discussed above. As such, Applicant respectfully requests reconsideration of the application and allowance of presently pending claims.

In the event that the Examiner finds remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, the Examiner is requested to contact the undersigned attorney by telephone at (801) 533-9800.

Dated this 4<sup>th</sup> day of November 2008.

Respectfully submitted,

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